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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

DETAILED ACTION

The Applicant's arguments, filed 10/08/96 have been thoroughly reviewed. Rejections and /or objections not reiterated from the previous office action are hereby withdrawn. The following rejections are either newly applied or reiterated. They constitute the complete set being presently applied to the present application. Response to Applicant's arguments follows.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-22,29,31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising probes of defined sequence, does not reasonably provide enablement for probes

recited by the function of hybridizing to ABL nucleic acid flanking sequence or BCR nucleic acid flanking sequence . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described in *In Re Colianni*, 195 USPQ 150 (CCPA 1977) and have been adopted by the Board of Patent Appeals and Interferences in *Ex Parte Forman*, 230 USPQ 546 (BPAI 1986). Among these factors are: the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the breadth of the claims, the amount of direction or guidance present, and the presence or absence of working examples.

The claims are drawn to compositions comprising a first and a second nucleic acid probe, said first probe hybridizing with an ABL nucleic acid flanking sequence and said second probe hybridizing with a BCR nucleic acid flanking sequence, said flanking sequences brought together by a chromosomal aberration. In further embodiments of the invention the sequences are recited as being able to hybridize to sequences that are *at least approximately* 800 kb apart in the aberrant chromosome or the

probes are juxtaposed as doublets if a chromosomal aberration in present. Additional claims further recite the nature of the fusion gene produced by said chromosomal aberration. The claims encompass diverse sequences given the recitation of ABL nucleic acid flanking sequence BCR nucleic acid flanking sequence. Part of the problem is that the claim might be interpreted in two ways. The first is that the flanking sequences are to flank ABL or BCR nucleic acids and then the claim encompasses sequences that are quite distant from ABL and BCR itself. The second way to interpret the claims is to assume that the sequences flank the breakpoint of the chromosomal aberration and are limited to ABL and BCR nucleic acids. In the first case, clearly the specification provides no guidance as to which of the vast genus of sequences that might be considered as ▒flanking▒, those which would be useful in in situ methods to detect the appropriate fusion genes, be diagnostic of the recited conditions, or be visible as doublets upon hybridization. However, even in the second scenario, where one assumes that the sequences are limited to ABL and BCR nucleic acids themselves, the applicant has taught defined regions of said nucleic acids and obtained only three probes which have the properties described as having the utility disclosed in the specification. The question then becomes, does the teachings of the specification in view of the art provide sufficient guidance to direct one to other probes within ABL and

BCR sequences that have the same disclosed utility. The art teaches BCR and ABL probes which are useful for the detection of these sequences in hybridization assays such as Southerns, however the detection of single copy sequences in situ was unpredictable in the art at the time that the invention was made and the detection of translocation breakpoints was further problematic. The applicant teaches that constraints on probes size are a matter of optimization and teaches an upper limit on probe size of about 200 kb, and teaches that flanking regions have to be approximately within 800 kb. The breakpoints were known and the sequences of both ABL and BCR were known in the art at the time that the invention was made, however while a variety of sequences might be useable as hybridization probes per se, the specification teaches that an essential requirement for success in an in situ method of detection is that the probe sequences must be about 800 kb appart. However, none of the defining features of the probes are recited in the claims and the claim that recites at least approximately 800 kb apart encompasses a diverse variety of species that are greater than 800 kb apart. Out of these species the number of nonworking embodiments far outnumbers the number of nonworking embodiments. Given the constraints on successfully detecting sequences involved in translocation breakpoints in an in situ method, it would require essentially a trial and error process to determine which of

number of species encompassed by the claims could detect the desired chromosomal aberrations.Therefore, it is the position of the examiner that it would require undue experimentation to perform the methods of the claims as broadly written.

3. Claims 1-33 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The following phrases render the claims vague and indefinite:

a. In claim 1, it is unclear what "an ABL nucleic acid flanking sequence or a "BCR nucleic acid flanking sequence" actually is (a sequence that flanks ABL or BCR, respectively or a sequence flanking a breakpoint of a chromosomal aberration that is an "ABL nucleic acid" or a "BCR nucleic acid").

b. Claim 12 is indefinite in reciting a "No." . The word should be spelled out or omitted.

c. In claim 16 the recitation of probes "designated" PEM12, c-H-able and MSB one is unclear in that it is unclear what aspect of a probe allows it to be "designated" in the recited manner. The claim might be amended by deleting the term "designated" . (Applicant is further reminded that if claiming the probes themselves , these are considered "biological material" and

since the sequences of the probes are unique they should be deposited under the terms of the Budapest Treaty) (see 37 CFR 1.801-1.809). See also claims 24-29.

d. Claim 23 is indefinite in that it is not clear what the metes and bounds of the probe are as it is not clear what sequences are enompassed bu the term 3' end. The claim might be amended to recite the range of nucleotide sequences to which the probe hybridizes.

e: Claim 31 is indefinite in the recitation of proteins "designated as" since it is unclear if the "designation of the proteins" means that they are in fact p190 and p210.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 8, 9, 11, 12,14, 17-20,22,23,30,31 are rejected under 35 U.S.C. 102(b) as being anticipated by Stephenson et al (USPAT 4681840, 1987). Stephenson et al. teaches synthetic oligonucleotides that are useful in the diagnosis of CML, teaching probes that are complementary to the two most common bcr-abl splice sites. Synthetic oligonucleotides are taught that are complementary to a sequence in bcr exon 2 and a sequence in abl exon 2. Thus the sequences are capable of hybridizing to

sequences that are ABL nucleic acid flanking sequences and BCR nucleic acid flanking sequences and are capable of detecting the p210 fusion gene. The probes/primers are capable of hybridizing to sequences that are at least approximately 800kb apart in the aberrant chromosome. The probes inherently possess the property of being capable of hybridizing (at least to some extent) with chromosomal DNA in situ in cells such as those which might be in interphase. The probes hybridize to the 5' "region" of chromosome 22, to the first exon "region (which is interpreted as sequences including and flanking the first exon" and the 3' "end" of the abl gene. The limitations of claims 17-20 are also met as the composition is defined in terms of its structural properties regardless of where a sample which it *might* be used to assay *might* be obtained.

Claims 2 and 29 are rejected under 35 U.S.C. § 103 as being unpatentable over Stephenson et al (USPAT 4681840, 1987). Stephenson et al. meets all of the limitations of the claims except for the teaching of a labelled probe or the teaching that the probes are provided in a kit. However, the labelling of probes for example with 32P was well known in the art at the time that the invention was made as was the convention of including compositions useful to perform a method in a kit, in order to provide such benefits of standardized, preweighed reagents in a convenient format. It therefore would have been prima facie obvious to one of ordinary skill in the art at the time that the invention was made to label the probes, for use in Southern analysis for example, or to provide the probes in a kit format to capitalize on the advantages that such a format provides.

No claims are allowed

Response to Applicants' arguments:

In order to proide a framework for this response, the examiner would like to indicate allowable subject matter at this point. The specific plasmid clones that Applicant has taught would be allowable, subject to their deposit according to the requirements of the Budapest treaty provided that the applicant claims these as such rather than as probes "designated as" (language that was removed from some of the claims but which remains in others). The Applicant has amended the claims to overcome the previous rejections made under 35 USC 112 second paragraph and 103 (Applicant' declaration was further considered probative as overcoming the rejection made in view of Gray et al.) , however Applicant's amendments have necessitated a new grounds of rejection under 35 USC 112 first and second paragraph and under 35 USC 102 (b) and 103. Part of the problem is that many of the features of the invention which Applicant argues as distinguishing over the art ,are not in fact recited in the claims, resulting in the art rejections and scope rejection applied above .The broad recitation of the claims encompasses a diverse number of species of nucleic acids which would not possess the essential features taught in the specification as necessary to enable the probes for the use for which they are intended - in situ hybridization to detect chromosomal abberrations, particularly translocation breakpoints diagnostic of ALL or diagnostic or prognsotic of both ALL and CML The number of nonworking

embodimetns of the claims, as written ,far outnumbers the working embodiments and it would require undue experimentation to select those sequences which have the desired and disclosed utility. With regards to rejections under 35 USC 102(e) and 103, Applicant is reminded that in a composition claim, one of skill in the art is not required to have the same motivation as the Applicant to assemble the recited components so long as the art provides a credible motivation to do so. In the instant case, the art provides the motivation to provide compositions of the recited probes for the purposes of Southern analysis of chromosomal abberrations, such as those involved in the recited pathologies and thus the claims as written do not distinguish over the cited art. Further limitations that might overcome the both the art and enablement rejections that might be added to the claims would be to recite the specific exons to which the probes hybridize to and to further clarify what "ABL nucleic acid flanking seuqneces" and "BCR nucleic acid flanking seuqneces" are.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

7. Papers related to this application may be submitted to Group 1800 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 305-7401. Please note that the faxing of such papers must conform with the notice to Comply published in the Official Gazette, 1096 OG 30 (Nov 15, 1989).

An inquiry regarding this communication should be directed to examiner Dianne Rees, Ph.D., whose telephone number is (703) 308-6565. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152

Calls of a general nature may be directed to the Group receptionist who may be reached at (703) 308-0196.

Dianne Rees
1/31/97

W. GARY JONES
SUPERVISORY PATENT EXAMINER
GROUP 1800
2/3/97